REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS & AMENDMENTS

Claims 1-32 were incorrectly indicated as pending in the Action of November 17, 2006. In fact, claims 1-21 and 23-33 are pending and claim 22 is cancelled.

Claims 1-2, 7-11 and 16-18 were examined on the merits and stand rejected.

Claims 3-6, 12-15, 19-21 and 23-33 were withdrawn as non-elected subject matter.

Claims 2 and 11 are cancelled without prejudice or disclaimer thereto. Applicants reserve the right to file a continuation or divisional application on any cancelled subject matter.

Claims 1 and 10 are amended to recite "the liver", as suggested by the Examiner.

Claims 1 and 10 are amended to recite the limitations of claims 2 and 11, respectively.

Claims 8, 10, 16-18 and 24 are amended to correct informalities.

No new matter has been added.

Claims 1, 3-10, 12-21 and 23-33 are pending upon entry of this amendment.

II. INFORMATION DISCLOSURE STATEMENTS

In item 2 on pages 2-3 of the Action, the Office referred to an IDS filed September 24, 2004. Please note that this IDS was actually filed September 27, 2004.

Also in item 2, the Office indicated that the Examiner is considering the references filed with the IDS of February 22, 2005. No IDS was submitted on February 22, 2005. However, Applicants' records indicate a Supplemental IDS was submitted on April 22, 2005. Accordingly, attached herewith is a copy of the IDS submitted April 22, 2005 with proof of prior submission in a copy of the postcard date-stamped by the Office.

III. CLAIM OBJECTIONS

In item 4 on pages 3-4 of the Action, claims 1, 7, 8, 10, 16 and 17 were objected to.

In particular, claims 1 and 10 were objected to for the recitation of "a liver". Accordingly, claims 1 and 10 have been amended to recite "the liver" as suggested by the Examiner. Applicants note that on the first line of page 4, the Office refers to claim 16. Applicants believe this sentence should instead refer to claim 10.

Claim 10 was further objected to for redundant recitations. Accordingly, claim 10 has been amended to remove this redundancy.

Claims 7 and 16 were objected to under 37 C.F.R. § 1.75(c) for failing to further limit the subject matter of the claims from which they depend. The Office contends that the specification teaches that a "proliferative human hepatocyte" has the ability to proliferate *in vitro* and therefore the independent claims from which claims 7 and 16 depend must already use proliferative human hepatocytes.

Applicants note that the "proliferative human hepatocytes" if claims 7 and 16 are a preferred embodiment of the present invention (see page 19, lines 16-26). In the instant invention, it is recommended to confirm the proliferative activity of hepatocytes prior to transplantation. However, such confirmation is not essential. Example 1 discloses human hepatocytes from a normal liver were transplanted into a mouse, in which said hepatocytes were not verified as having proliferative activity. In other words, human hepatocytes from normal liver may be proliferative in the mouse but are not necessarily proliferative human hepatocytes as defined in the specification on page 19. Applicants therefore respectfully note that claims 7 and 16 do further limit the claims from which they depend.

Claims 8 and 17 were objected to for the recitation of "with forming colony". Accordingly, claims 8 and 17 have been amended to recite "to form a colony".

In light of the above amendments to the claims, the objection to claims 1, 7, 8, 10, 16 and 17 is now inapplicable and should be withdrawn.

IV. WRITTEN DESCRIPTION REJECTION

In item 5 on pages 5-7 of the Action, claims 1-2, 7-11 and 16-18 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification lacks written description support for the genus comprising feeding anything under conditions as being protected from the attack by human complement and administering any complement inhibitor.

This rejection is believed to be overcome by the foregoing amendments for the following reasons.

Claims 2 and 11 are cancelled. Further, independent claims 1 and 10 are amended to include the limitations of claims 2 and 11, respectively. In particular, these claims are amended to recite that the mice transplanted with human hepatocytes are protected from complement associated tissue damage by either (1) administering an effective amount of a complement inhibitor to such mice, or (2) such mice are progeniture mice obtained by mating an immunodeficient hepatopathy mouse and a decay-accelerating factor (DAF/CD55) transgenic mouse.

Applicants note that "administration of an effective amount of a complement inhibitor" in claims 1 and 10 have written description support in the specification on page 16, line 6 to page 17, line 17. Further, use of complement inhibitors to protect against damage by human complement from human hepatocytes is well known in the art as demonstrated by two attached references (Yong-Guang Yang et al. and Tamura et al.). Also, immunodeficient mice and hepatopathy mice are known in the art as also indicated in attached references (Spanopoulou et al., Shinkai et al., Ito et al., Shultz et al., Hioki et al. and Mosier et al.). DAF/CD55 mice are known in the art as indicated in Bryce et al and Murakami et al (attached). Thus, a person of skill in the art would understand based on the specification and the knowledge in the art that the Applicants had possession of the invention of the amended claims.

For the foregoing reasons, Applicants respectfully suggest this rejection under 35 U.S.C. § 112, first paragraph, for lack of written description support, as applied to the amended claims,

is untenable and should be withdrawn.

V. ENABLEMENT REJECTION

In item 6 on pages 8-16, claims 1-2, 7-11 and 16-18 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification is not enabled. In particular, the Examiner only considered the rejected claims enabled for a method of proliferating human hepatocytes comprising transplanting proliferative human hepatocytes into the liver of a uPA-Tg/SCID immunodeficient hepatopathy mouse comprising a homozygous insertion of a uPA-Tg into the genome of a homozygous SCID mouse, administering an effective amount of the complement inhibitor, Futhan, to protect against tissue damage associated with human complement produced by human hepatocytes, proliferating said human hepatocytes in the liver of said mouse, isolating human hepatocytes from the liver of said mouse transplanted with human hepatocytes, and transplanting the human hepatocytes isolated from the liver of said mouse into other uPA-Tg/SCID immunodeficient hepatopathy mice comprising a homozygous insertion of a uPA-Tg into the genome of a homozygous SCID mouse.

This rejection is respectfully traversed as applied to the amended remaining claims for the following reasons.

As noted above, claims 1 and 10 are amended to recite that the mice transplanted with human hepatocytes are protected from complement tissue damage by either (1) administering an effective amount of a complement inhibitor to such mice, or (2) such mice are progeniture mice obtained by mating an immunodeficient hepatopathy mouse and a decay-accelerating factor (DAF/CD55) transgenic mouse.

"Immunodeficient hepatopathy mouse" should not be limited to the "uPA-Tg/SCID mouse". As described on page 17, line 19 to page 18, line 18, the immunodeficient hepatopathy mouse is available as a progeniture mouse by mating between a genetically immunodeficient mouse and a genetically hepatopathy mouse. Such mice are well known in the art, and a skilled

artisan can practice the present invention by using a known immunodeficient mouse and a known hepatopathy mouse. For example, please see the attached articles for known immunodeficient mice (Spanopoulou et al., Shinkai et al., Ito et al., Shultz et al., Hioki et al. and Mosier et al.). The main requirement for the "immunodeficient hepatopathy mouse" in the present invention is a hepatopathy mouse in which native hepatocytes are dysfunctional, and also an immunodeficient mouse which does not reject transplanted cells from heterogeneous animals (see page 17, lines 19-23). Thus, it would not be difficult for one skilled in the art to prepare such a mouse by using available materials and methods.

Further, the Office's understanding of "a **homozygous** insertion of a uPA-Tg in the genome" is incorrect. The uPA-Tg is one means for hepatopathy, as described above. A genetic manipulation for hepatopathy such as a **hemizygous** gene insertion is possible (see Example 4 on pages 39-40 of the specification).

The means for "protecting against tissue damages associated with human complement produced by the human hepatocytes" are not limited to administration of Futhan. In this regard, the specification describes some means in detail at page 16, line 6 to page 17, line 17. The means described therein for complement inhibition are well known in the art. Attached to this reply are articles about complement inhibitors FOY, Foipan and cobra toxin (Yong-Guang Yang et al. and Tamura et al.), as well as for DAF/CD55 (Bryce et al. and Murakami et al). Regarding complement inhibitors, these agents are commonly used in transplantation technology and are therefore useable in the present invention in the same manner.

For the above reasons, Applicants respectfully suggest that this rejection, as applied to the remaining amended claims, is untenable and should be withdrawn.

VI. INDEFINITENESS REJECTION

Claims 2, 8, 9, 11, 17 and 18 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite for the reasons set forth on page 16-17.

Claims 2 and 11 are cancelled. Claims 8 and 17 are amended to recite "to form a colony". Thus, Applicants respectfully submit this rejection is overcome.

VII. ANTICIPATION REJECTIONS

On pages 17-19 of the Action, claims 1, 7, and 8 were rejected under 35 U.S.C. § 102(b) as anticipated by Brown et al. (Hepatology, Vol. 31, pp. 173-181, 2000). Further, in item 8 on pages 19-21 of the action, claims 1, 7 and 8 are rejected under 35 U.S.C. § 102(b) as being anticipated by Dandri et al. (Hepatology, Vol. 33, pp. 981-988, April 2001). Finally, in item 9 on pages 22-24, claims 1, 7 and 8 were rejected under 35 U.S.C. § 102(e) as anticipated by Kneteman et al. (US 6,509,514).

Claim 1 has been amended to recite the limitations of claim 2, which was not anticipated by the cited references. Thus, Applicants respectfully submit these rejections are overcome.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

Chise MUKAIDANI et al.

By: _____
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Applicants

WMC/WRS/mjw
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
May 17, 2007

ATTACHMENTS:

1. Copy of Supplemental IDS with Form PTO-1449 submitted April 22, 2005 with date-stamped postcard, and

2. Ten supplemental references:

   a. Bryce, J. W. et al. Transplantation, 61: 582-586, 1996.

   b. Murakami, H. et al. Immunology, 201: 583-597, 1999/2000.

   c. Yong-Guang Yang, A. M. et al. Transplantation, 69: 163-190, 2000.

   d. Tamura Y. et al. Biochem. Biophys. Acta. 484: 417-422, 1977.

   e. Spanopoulou, E. et al. Genes and Development, 8: 1030-1042, 1994.

   f. Shinkai,Y. et al. Cell, 68: 855-867, 1992.

   g. Ito M. et al. Blood, 100: 3175-3182, 2002.

   h. Shultz, L. D. The Journal of Immunology, 154: 180-191, 1995.

   i. Hioki, K. et al. Exp. Anim. 50: 67-72, 2001.

   j. Mosier, D. E. et al. J. Exp. Med. 177: 191-194, 1993.

COPY

ATTY DOCKET #: 2004_1544A
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Applicant: Chise MUKAIDANI et al.
Serial No.: 10/509,032
Filing Date: February 9, 2005
Title: A METHOD OF PROLIFERATING HUMAN HEPATOCYTES AND A METHOD FOR OBTAINING HUMAN HEPATOCYTES

Due Date:

Receipt of the following papers is acknowledged:

SUPPLEMENTAL IDS, PTO-1449 FORM WITH 8 REFERENCES.

Date: April 22, 2005 **Attorney:** WMC/dlk **[Check No._____]** **e Date:**

SUPPLEMENTAL IDS, PTO-1449 FORM WITH 8 REFERENCES.

Date: April 22, 2005 **Attorney:** WMC/dlk **[Check No._____]**